PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Effects of a 6 months self-rehabilitation program in addition to botulinum toxin injections and conventional physiotherapy on limitations of patients with spastic hemiparesis following stroke (ADJU-TOX): protocol study for a randomised controlled, investigator blinded study.
AUTHORS	Bonnyaud, Celine; Gallien, Philippe; Decavel, Pierre; Marque, Philippe; Aymard, Claire; Pellas, Frédéric; Isner, Marie Eve; Boyer, François; Muller, François; Daviet, Jean-Christophe; Dehail, Patrick; Perrouin Verbe, Brigitte; Bayle, Nicolas; Coudeyre, Emmanuel; Perennou, Dominic; Laffont, Isabelle; Ropers, Jacques; Saidji, Nabila-Yasmine; Bensmail, Djamel; Roche, Nicolas; ADJU-TOX, group

VERSION 1 – REVIEW

REVIEWER	Giovanni Abbruzzese DINOGMI - University of Genoa (Italy)
REVIEW RETURNED	23-Dec-2017

GENERAL COMMENTS	This is a multicentre, prospective, RC – SB study to compare in chronic hemiparetic stroke patients with spasticity the effects of the following two treatments: 1. botulinum toxin injection (two injections with an interval of 3 months) + usual physiotherapy (conventional treatment); 2. conventional treatment + a 6 months self-rehabilitation program. The main goal is to assess, on a large cohort of patients, the effects of a self-rehabilitation in addition of usual treatments over a long period of time. The study is well designed and presented. Methodology and sample size are sound. General Comment In the background and in the discussion, the Authors say that upper limb spasticity is “associated with active motor dysfunction and disabilities to use arm in daily living activities”. Furthermore, they say that lower limb spasticity “reduce displacements and participation of patients with stroke”. Therefore, they focused the attention on spasticity, but it is well known that spasticity is only one of the positive phenomena of the upper motor neuron syndrome, which include spastic dystonia and spastic co-contraction (see, for instance: Marinelli et al. 2017). The latter are much more disabling that spasticity itself and represent the true target of botulinum toxin treatment. In the background and in the discussion this point should be clarified. Specific points

	- In the self-rehabilitation program, the patients can choose to carry out all the exercises at once (30 minutes) or each dimension at a different moment of the day (3 times 10 minutes). I think that this possibility could introduce unwanted variability in the results. Therefore, I suggest that the exercises should be conducted in the same session. - In the Goal Attainment Scaling (GAS), the patient's initial state is assigned a score of -1. Instead, the initial state should be assigned as score 0 and, consequently, 0 means no effect, +1 improvement, +2 marked improvement; -1 worsening; -2 marked worsening. - In the sample size estimation, the Authors should explain why they chose a target proportion of 90% in the self-rehabilitation group.

REVIEWER	Susan Hillier University of South Australia
REVIEW RETURNED	02-Jan-2018

GENERAL COMMENTS	Please find comments and queries as follows: Abstract 1. Stroke not stoke patients. And I would strongly suggest putting the person first e.g. person with stroke. 2. The abstract introduction is too long and doesn't flow: please shorten and rewrite to be more concise and logical. 3. The aim is hard to understand - please rewrite 4. five visits for what? clarify or delete. 5. in the methods it becomes clear you are looking at the addition of self-rehab to Physio/botox combo. I am not sure this is an important question. Strength and limitation dot points 1. please rewrite all for more accurate English. background 1. third HIGHEST case of mortality. and why just cite industrialised countries. be more internationally inclusive. 2. line 37 - what does the "respectively refer to? 3. there is a lot of unusual English in the background - line 3 on page 7 is particularly difficult to comprehend. 4. You are ssetting up the background to compare BTI with PT in some ways. But really you are looking at a way to increase intensity of PT via a home program. Therefore your background should focus more on intensity and self-management. 5. page 9 - again the aim is poorly worded - please rewrite for clarity. Methods 1. Subjects - please ensure future tense as this is a protocol e.g. inclusion criteria WILL BE or even ARE. 2. why criterion that they have had botox before? 3. how will you determine that are able to participate in a self-rehab program? 4. if you exclude those "unlikely to adhere to the study" then your aim of feasibility and tolerability is not going to be answered. How would you operationalize this criterion anyway? 5. why stretching when there is no evidence for it? 6. please rewrite the methods in line with the CONSORT statement and use their flow chart 7. use a different term than thymic state - this is not used in regular English. I think you mean mood. 8. Missingness is not a word. I think you mean missing data. 9. I think you need to be careful about interpreting the evidence of a beneficial effect of adjuvant therapies to BTI - it is more that BTI itself has limited evidence.

	10. which international trial register will this be lodged with? 11. some of the references are old - please update.

VERSION 1 – AUTHOR RESPONSE

Reviewer(s)' Comments to Author:

Reviewer: 1
Reviewer Name: Giovanni Abbruzzese
Institution and Country: DINOGMI - University of Genoa (Italy)
Please state any competing interests or state 'None declared': None

Please leave your comments for the authors below
This is a multicentre, prospective, RC – SB study to compare in chronic hemiparetic stroke patients with spasticity the effects of the following two treatments: 1. botulinum toxin injection (two injections with an interval of 3 months) + usual physiotherapy (conventional treatment); 2. conventional treatment + a 6 months self-rehabilitation program.
The main goal is to assess, on a large cohort of patients, the effects of a self-rehabilitation in addition of usual treatments over a long period of time.
The study is well designed and presented. Methodology and sample size are sound.

We are very grateful to Reviewer 1 for carefully reading our manuscript and communicating favorable comments to us.
Point-by-point replies are provided below.

General Comment
In the background and in the discussion, the Authors say that upper limb spasticity is "associated with active motor dysfunction and disabilities to use arm in daily living activities". Furthermore, they say that lower limb spasticity "reduce displacements and participation of patients with stroke". Therefore, they focused the attention on spasticity, but it is well known that spasticity is only one of the positive phenomena of the upper motor neuron syndrome, which include spastic dystonia and spastic co-contraction (see, for instance: Marinelli et al. 2017). The latter are much more disabling that spasticity itself and represent the true target of botulinum toxin treatment. In the background and in the discussion this point should be clarified.
This point has been modified as suggested the reviewer.
Please see p2 in the background: "Among impairments, positive signs of the upper motor neuron syndrome (upper-limb spasticity, co-contraction and dystonia) are associated with active motor dysfunction and disabilities to use arm in daily living activities [7], [8], [9]. Gait limitations following symptoms of upper motor neuron syndrome reduce also displacements and participation of patients with stroke [21], [22]."

Please see p15 in discussion: “To potentiate the effects of BTI and reduce consequences of hypertonia following stroke (spasticity, spastic dystonia, spastic co-contraction), rehabilitation approach could be proposed to patients. In this context, some studies have evaluated the additional benefit of adjuvant therapies [62], [63].”

Specific points

- In the self-rehabilitation program, the patients can choose to carry out all the exercises at once (30 minutes) or each dimension at a different moment of the day (3 times 10 minutes). I think that this possibility could introduce unwanted variability in the results. Therefore, I suggest that the exercises should be conducted in the same session.

As suggested the reviewer, the exercises will be conducted in a single session of 30minutes. This point has been corrected in the methods section.

Please see p8: “The patients will be instructed to carry out a session of exercises during 30 minutes (including 10 minutes within each dimension), each day, 7 days per week, 6 months of their participation in the study.”

- In the Goal Attainment Scaling (GAS), the patient's initial state is assigned a score of -1. Instead, the initial state should be assigned as score 0 and, consequently, 0 means no effect, +1 improvement, +2 marked improvement; -1 worsening; -2 marked worsening.

We agree with the reviewer that his suggested scoring would make sense but the scoring proposed in the present study is in accordance with the original Goal Attainment Scaling scoring.

Thomas J. Kiresuk and Robert E. Sherman were the first to propose use the Goal Attainment Scaling in 1968 for evaluating health programs. Their outcome values were: -2 for Most unfavorable treatment outcome, -1 for less than expected success with treatment, 0 for expected level of treatment success, 1 for more than expected success with treatment and 2 for best anticipated treatment success.

In 2006, Stephen Ashford and Lynne Turner-Stokes proposed the Goal attainment for spasticity management using botulinum toxin and found that GAS provides a useful measure of functional gains in response to treatment with botulinum toxin. Similarly -1 was the baseline score allocated, If the goal was achieved as predicted, this scored 0, achievement above the level predicted was scored at +1 (‘somewhat better than expected’) or +2 (‘much better than expected’), no change or achievement below the expected level was scored as -1, and a worsening of the target function was scored as -2.

[Kiresuk TJ, Sherman RE. Goal attainment scaling: A general method for evaluating comprehensive community mental health programs. Community Ment Health J 1968;4:443–53.]

[Ashford S, Turner-Stokes L. Goal attainment for spasticity management using botulinum toxin. Physiother Res Int 2006;11:24–34.]

This choose of scoring was specified this in the text for this to be explicit for the reader.

Please see p9: “As suggested in the original scoring of the GAS and in studies using this evaluation to assess spasticity management with BTI, the patient’s initial state is assigned a score of -1 [48], [56]. If

the goal is attained, a score of 0 will be assigned. Improvement above what is expected (somewhat better than expected = +1 or much better than expected = +2) as well as worse than expected (-2) will also be defined."

- In the sample size estimation, the Authors should explain why they chose a target proportion of 90% in the self-rehabilitation group.

Data from the literature allow us to set the target for the control group receiving botulinum toxin alone [Turner-Stokes 2013, Demetrios 2014]. This target is a proportion of 75% of patients who achieve their primary treatment goal. Based on this data, the most reasonable target proportion for the self-rehabilitation group (self-rehabilitation in adjunction to the botulinum toxin injection) was 90% since the adjunction of self-rehabilitation is supposed to further improve patients than botulinum toxin alone. Previous studies showed indeed better improvements when rehabilitation is proposed to optimize the effects of botulinum toxin injections [Roche 2015, Mills 2016, Sheean 2010]. The threshold of 90% appears to be a reasonable target proportion relatively superior to the 75% taking into account variability due to patients' heterogeneity. This target could be considered as the minimally clinically relevant difference between a conventional improvement (75%) and a better improvement due to the addition of intensive exercices (90%). These target proportions allowed us to calculate the sample size.

Please see p13: "Based on a usual effectiveness of 75% in the control group, a target proportion of 90% in the self-rehabilitation group (supposing further improvements for this group, threshold relatively superior to 75%, reasonable and clinically relevant), a two-tailed test at a threshold of 5% and a power of 80%, a sample of 100 subjects per group is required [62]."

[Roche N, Zory R, Sauthier A, Bonnyaud C, Pradon D, Bensmail D. Effect of rehabilitation and botulinum toxin injection on gait in chronic stroke patients: a randomized controlled study. J Rehabil Med. 2015 Jan;47(1):31-7.]
[Mills PB, Finlayson H, Sudol M, O'Connor R. Systematic review of adjunct therapies to improve outcomes following botulinum toxin injection for treatment of limb spasticity. Clin Rehabil. 2016 Jun;30(6):537-48.]

Reviewer: 2
Reviewer Name: Susan Hillier
Institution and Country: University of South Australia
Please state any competing interests or state 'None declared': None declared

We are very grateful to Reviewer 2 for carefully reading our manuscript and communicating favorable comments to us.
Point-by-point replies are provided below.

Please leave your comments for the authors below

Please find comments and queries as follows:

Abstract

1. Stroke not stoke patients. And I would strongly suggest putting the person first e.g. person with stroke.

Sentence has been corrected as suggested the reviewer.

Please see p2 and others p4, p5: “patients with stroke”

2. The abstract introduction is too long and doesn't flow: please shorten and rewrite to be more concise and logical.

3. The aim is hard to understand - please rewrite

The abstract introduction and the aim have been rewritten.

Please see p2: “Home-based self-rehabilitation programs combined with botulinum toxin injections (BTI) appear to be a relevant approach to increase the recommended intensive rehabilitation of spastic patients following a stroke. The literature highlights a lack of evidence of beneficial effects of this adjuvant therapy to reduce limitations of patients with stroke. The aim of this study is to assess the effects of a 6-months self-rehabilitation program in adjunction to BTI, in comparison with BTI alone, to reduce limitations of spastic patients with stroke.”

4. five visits for what? clarify or delete.

The procedure of the protocol has been specified rather than the number of visits

Please see p2: “All patients will benefit from two successive BTI (3 months apart) and, patients randomized in the self-rehabilitation group will perform in adjunction 6 months of self rehabilitation at home.”

5. in the methods it becomes clear you are looking at the addition of self-rehab to Physio/botox combo. I am not sure this is an important question.

Patients with stroke are routinely injected every 3 months with botulinum toxin to reduce their awkward spasticity. Studies showed positive effects of these injections on spasticity, pain, stiffness and gait kinematics but functional improvements are moderate or non-significant for lower-limb and upper-limb [Francisco 2007, Elia 2009, Foley 2013, Demetrios 2013, Bensmail 2010, Hutin 2010, Robertson 2009]. It is also widely recognized that intensive rehabilitation is the decisive factor for the functional improvement of patients with stroke [Langhorne 2009, 2011 Lancet Review]. Training 3 to 7 days per week and 20 to 60 minutes per day is indeed recommended for these patients [Gordon 2004]. However French patients with stroke have an average of 1.7 physiotherapist visits per week only [Tosun 2010] and are rarely involved in physical activities. To potentiate effects of spasticity management with BTI and induce functional improvements, oriented self-rehabilitation appears an interesting alternative in a system of care financially constrained. It is indeed suggested that the clinical use of Botulinum toxin can not be an isolated intervention but should be considered as a

possible option integrated within a rehabilitation programme [Paci 2017]. This approach is intended to respond to reviews that recommend studies with large sample size to highlight functional effects of spasticity management [Elia 2009, Demetrios 2013]. A recent systematic reviews report also that there is insufficient evidence on adjunctive therapies following Botulinum toxin [Moore 2015].

[Bensmail D, Robertson JV, Fermanian C, Roby-Brami A. Botulinum toxin to treat upper-limb spasticity in hemiparetic patients: analysis of function and kinematics of reaching movements. Neurorehabil Neural Repair. 2010 Mar-Apr;24(3):273-81.]
[Demetrios M, Khan F, Turner-Stokes L, Brand C,McSweeney S.Multidisciplinary rehabilitation following botulinum toxin and other focal intramuscular treatment for post-stroke spasticity. Cochrane Database of Systematic Reviews 2013, Issue 6. Art. No.: CD009689.]
[Elia AE, Filippini G, Calandrella D, Albanese A. Botulinum neurotoxins for post-stroke spasticity in adults: a systematic review. Mov Disord. 2009 Apr 30;24(6):801-12.]
[Foley N, Pereira S, Salter K, Fernandez MM, Speechley M, Sequeira K, Miller T, Teasell R. Treatment with botulinum toxin improves upper-extremity function post stroke: a systematic review and meta-analysis. Arch Phys Med Rehabil. 2013 May;94(5):977-89.]
[Francisco GE. Botulinum toxin for post-stroke spastic hypertonia: a review of its efficacy and application in clinical practice. Ann Acad Med Singapore. 2007 Jan;36(1):22-30.]
[Gordon NF, Gulanick M, Costa F, Fletcher G, Franklin BA, Roth EJ, Shephard T; American Heart Association Council on Clinical Cardiology, Subcommittee on Exercise, Cardiac Rehabilitation, and Prevention; the Council on Cardiovascular Nursing; the Council on Nutrition, Physical Activity, and Metabolism; and the Stroke Council. Physical activity and exercise recommendations for stroke survivors: an American Heart Association scientific statement from the Council on Clinical Cardiology, Subcommittee on Exercise, Cardiac Rehabilitation, and Prevention; the Council on Cardiovascular Nursing; the Council on Nutrition, Physical Activity, and Metabolism; and the Stroke Council. Stroke. 2004 May;35(5):1230-40.]
[Hutin E, Pradon D, Barbier F, Gracies JM, Bussel B, Roche N. Lower limb coordination in hemiparetic subjects: impact of botulinum toxin injections into rectus femoris. Neurorehabil Neural Repair. 2010 Jun;24(5):442-9.]
[Langhorne P, Coupar F, Pollock A. Motor recovery after stroke: a systematic review. Lancet Neurol. 2009 Aug;8(8):741-54]
[Langhorne P, Bernhardt J, Kwakkel G. Stroke rehabilitation. Lancet. 2011 May 14;377(9778):1693-702]
[Moore EJ, Banky M, Olver J, Bryant AL, Williams G. The effectiveness of therapy on outcome following (BoNT-A) injection for focal spasticity in adults with neurological conditions: A systematic review. Brain Inj. 2015;29(6):676-87.]
[Paci M. Botulinum toxin after stroke: A functional point of view. Journal of the Neurological Sciences 382 (2017) 185–186]

[Robertson JV, Pradon D, Bensmail D, Fermanian C, Bussel B, Roche N. Relevance of botulinum toxin injection and nerve block of rectus femoris to kinematic and functional parameters of stiff knee gait in hemiplegic adults. Gait Posture. 2009 Jan;29(1):108-12.]
[Tosun, J., 2010. Etude de l'autonomie des patients hémiparétiques au stade chronique d'un accident vasculaire cérébral en médecine générale. Créteil.]

Please rewrite all for more accurate English.
The manuscript has been read by a native English person

background

1. third HIGHEST case of mortality. and why just cite industrialised countries. be more internationally inclusive.
The sentence has been changed to have an international vision.
Please see p4: "Stroke is the second highest cause of death worldwide and the fourth leading cause of lost productivity (disability-adjusted life years) according to the World Health Organization."

2. line 37 - what does the "respectively refer to?
The sentence has been deleted for better understanding. Physiotherapy and spasticity management have been separated in two different paragraphs.
Please see p4

3. there is a lot of unusual English in the background - line 3 on page 7 is particularly difficult to comprehend.
The sentence has been changed.
Please see p6: "Some authors state that conventional outcome measures used in these previous studies are not suitable [43], [48], [49]. They suggest using an individually based approach such as the Goal Attainment Scaling (GAS) which showed significant improvements following BTI [48], [49]."

4. You are ssetting up the background to compare BTI with PT in some ways. But really you are looking at a way to increase intensity of PT via a home program. Therefore your background should focus more on intensity and self-management.

We agree with the reviewer that the study proposes to increase the intensity of physiotherapy via a home program to optimize effects following BTI. However it should be specified that exercises of the program are oriented, specifically chosen to correspond to the Primary Treatment Goal (corresponding also to the injected muscles with botulinum toxin) which is different to increase the time of physiotherapy without oriented and standardized program.
These last years, several studies and two recent systematic reviews analyzed the effectiveness of therapy on outcome following BTI in adults with neurological conditions [Carda 2011, Santamato 2015, Sun 2010, Moore 2015, Mills 2016]. In their review, Mills et al found evidence to suggest that adjunct therapies may improve outcomes following botulinum toxin injection although outcome

measures were highly variable, while Moore et al showed that there is insufficient evidence to support or refute this effectiveness, mainly due to the low power of studies [Moore 2015, Mills 2016].
The relevant question studied by these authors is Does the adjunction of a specific therapy to BTI is effective and better than BTI alone to improve patients' capacities. In this context, in view of these authors' recommendations, it appears relevant to propose a study with a large sample size and robust methodology to investigate this question with personalized treatment goals, as recently suggested and, involving a complete rehabilitation program. Nevertheless we agree that the intensity of rehabilitation is indirectly increased, but specifically oriented.

After generalities about stroke and consequences, the first part of the background exposes the interest of an intensive oriented rehabilitation and suggests self-rehabilitation to answer to this problematic. Please see p4, for example "it has been demonstrated that the intensity, the frequency and the specificity (to train specifically the task to improve) of physiotherapy is positively correlated with recovery"; "many studies highlighted that improvements continue and are effective in chronic patients with stroke who follow intensive active rehabilitation";
Some sentences have been modified: "A self-rehabilitation program appears a relevant approach to increase this intensive oriented needed rehabilitation and further improve recovery of these patients."
Sentences (involving Goal Attainment Scaling) have been transferred in methods section to further target the introduction on intensive rehabilitation and adjunctive therapies to BTI.
The two last paragraphs have been modified (with deletions and additions) to take into consideration the comment of the reviewer.
Please see p6: "To increase intensive oriented rehabilitation following BTI would be indeed relevant. (…). Results of these pilot studies with restricted sample suggest effectiveness of adding intensive therapy following BTI in patients with stroke, which corresponds to the conclusions of two recent reviews [55], [56]. These reviews recommend however further study with large sample size, long duration and robust methodology."

[Carda S, Invernizzi M, Baricich A, Cisari C. Casting, taping or stretching after botulinum toxin type A for spastic equinus foot: a single-blind randomized trial on adult stroke patients. Clin Rehabil. 2011 Dec;25(12):1119-27.]
[Mills PB, Finlayson H, Sudol M, O'Connor R. Systematic review of adjunct therapies to improve outcomes following botulinum toxin injection for treatment of limb spasticity. Clin Rehabil. 2016 Jun;30(6):537-48.]
[Moore EJ, Banky M, Olver J, Bryant AL, Williams G. The effectiveness of therapy on outcome following (BoNT-A) injection for focal spasticity in adults with neurological conditions: A systematic review. Brain Inj. 2015;29(6):676-87.]
[Santamato A, Micello MF, Panza F, Fortunato F, Picelli A, Smania N, Logroscino G, Fiore P, Ranieri M. Adhesive taping vs. daily manual muscle stretching and splinting after botulinum toxin type A injection for wrist and fingers spastic overactivity in stroke patients: a randomized controlled trial. Clin Rehabil. 2015 Jan;29(1):50-8.]

[Sun S-F, Hsu C-W, Sun H-P, Hwang C-W, Yang C-L and Wang J-L. Combined botulinum toxin type A with modified constraint-induced movement therapy for chronic stroke patients with upper extremity spasticity: A randomized controlled study. Neurorehabil Neural Repair 2010; 24(1): 34–41.]

5. page 9 - again the aim is poorly worded - please rewrite for clarity.
The aim has been rewritten.
Please see p6: “The aim of this study is to assess the effects of a 6-months self-rehabilitation program in adjunction to BTI, in comparison with BTI alone, to reduce limitations of spastic patients with stroke.”

Methods

1. Subjects - please ensure future tense as this is a protocol e.g. inclusion criteria WILL BE or even ARE.
Thank you for your correction, sentences have been corrected
Please see p8: “The inclusion criteria are..” ; “The exclusion criteria are…”

2. why criterion that they have had botox before?
Most chronic patients with stroke followed in medical consultations in hospitals involved in this study regularly benefit of botulinum toxin injections (BTI) to reduce their spasticity and awkward consequences. Including, in this study, most of patients regularly injected why botulinum toxin and some patients injected for the first time would increase, in our opinion, heterogeneity of our sample.
It is indeed suggested that BTI generates synaptic plastic reorganization allowing motor re-learning if coupled with sustained activity-based, goal-oriented training programs [Li 2017]. BTI induce muscles modifications and, modifications of the movement such as increase of peak knee flexion during swing phase of the gait after rectus femoris injection [Robertson 2009] and, improvement of movement direction during reach-to-grasp after upper-limb injections [Bensmail 2010]. It could thus be proposed that patients regularly injected appropriate gradually the benefits of injections, with training.
Santamato et al (2017) found for example that 45% of patients with stroke considered as “moderate improvement” the global effect after eight toxin injection sets compared to the 20% after the first injection set. Similarly, Bensmail et al (2010) assessed the effects of two repeated toxin injections on reach-to-grasp and grasping objects in patients with stroke. They showed that peak hand velocity increased after the first BTI and continue to increase significantly between the first and the second injection. The frequency of the normal direction increased also from 60 to 69% from the first to the last session. Moreover, Tok et al (2011) showed muscle architecture changes following BTI in patients with stroke and suggested that long-term effects of BTI need further studies since modifications could be different in patients firstly injected and patients regularly injected [Tok 2011].
It appears thus that the “first-injected” patients may not have the same modifications that patients regularly injected, which could imply a bias in the study.
Another argument is that botulinum toxin injections are often used in acute phase following stroke since it is recommended by guidelines as a first-line treatment for adults with spasticity [Royal College

of Physicians, British Society of Rehabilitation Medicine 2009, Wissel 2009, Simpson 2016]. Patients injected for the first time may be more acute than those who are regularly injected, which would tend towards more heterogeneity of our sample is some are included.

[Bensmail D, Robertson JV, Fermanian C, Roby-Brami A. Botulinum toxin to treat upper-limb spasticity in hemiparetic patients: analysis of function and kinematics of reaching movements. Neurorehabil Neural Repair. 2010 Mar-Apr;24(3):273-81.]
[Li S. Spasticity, Motor Recovery, and Neural Plasticity after Stroke. Frontiers in Neurology 2017; 8:120.]
[Robertson JV, Pradon D, Bensmail D, Fermanian C, Bussel B, Roche N. Relevance of botulinum toxin injection and nerve block of rectus femoris to kinematic and functional parameters of stiff knee gait in hemiplegic adults. Gait Posture. 2009 Jan;29(1):108-12.]
[Royal College of Physicians, British Society of Rehabilitation Medicine, Chartered Society of Physiotherapy, Association of Chartered Physiotherapists Interested in Neurology. Spasticity in adults: management using botulinum toxin. National guidelines. 2009]
[Santamato A, Panza F, Intiso D, Baricich A, Picelli A, Smania N, Fortunato F, Seripa D, Fiore P, Ranieri M. Long-term safety of repeated high doses of incobotulinumtoxinA injections for the treatment of upper and lower limb spasticity after stroke. J Neurol Sci. 2017 Jul 15;378:182-186.]
[Simpson DM, Hallett M, Ashman EJ, et al. Practice guideline update summary: Botulinum neurotoxin for the treatment of blepharospasm, cervical dystonia, adult spasticity, and headache: Report of the Guideline Development Subcommittee of the American Academy of Neurology. Neurology 2016;86:1818-1826.]
[Tok F, Ozçakar L, Safaz I, Alaca R. Effects of botulinum toxin-A on the muscle architecture of stroke patients: the first ultrasonographic study. J Rehabil Med. 2011 Nov;43(11):1016-9.]
[Wissel J, Ward AB, Erztgaard P, et al. European consensus table on the use of botulinum toxin type A in adult spasticity. J Rehabil Med 2009;41:13-25.]

3. how will you determine that are able to participate in a self-rehab program?
To be able to participate to the program, patients should not have severe comprehension deficit, apraxia or anosognosia. These criteria will be check at the inclusion visit. These cognitive dysfunctions have been added in the exclusion criteria.
Please see p8: “The exclusion criteria are… comprehension deficit with score to the Boston Diagnostic Aphasia Examination <3, severe apraxia or anosognosia,”
Also, to ensure that patients would be able to practice exercises alone at home, a test session of training will be done at the hospital with the therapist. The sentence p10 has been completed “All the exercises will be taught to the patient by a physiotherapist who is not involved in the patients follow-up, during V1, following randomisation to the SR group as well as during V3 (second BTI), if the exercises are changed. The therapist will make sure that the patient is able to perform the exercises alone.”
These precisions have been added in the text.

Please see p8: able to participate in a self-rehabilitation program (cognitive functions and test session with the therapist)

4. if you exclude those "unlikely to adhere to the study" then your aim of feasibility and tolerability is not going to be answered. How would you operationalize this criterion anyway?
To participate to the study, patients are informed of the procedure with explanations of what the two groups induce. Are included in the study only patients who say they are ready to perform rehabilitation sessions at home.
Our aim of feasibility and tolerability concerned patients included and randomized in the self-rehabilitation group. It is indeed quite conceivable that patients declare themselves ready to carry out the complete program but do not perform it as a whole.
For example, in a previous pilot study (Roche 2015), patients with stroke had to perform 30 minutes every day of self-rehabilitation at home during 1 month. Results showed that of 19 patients, 16 performed the programme between 5 and 7 days per week, one patient performed the programme 3 days per week and 2 reported that they performed it occasionally (fewer than 2 days/week). Similarly this study included patients who declared themselves, initially, able to perform the programme 30 min per day, 7 day /7, during one month. There may be a gap between what patients say at the beginning of a study and what they are really doing.
Also, the duration of the present study is quite long for patients (6 months) and the program is relatively intensive with 30min per day, every day during 6 months. It is possible that some patients initially motivated to complete the full self-rehabilitation program will wilt over time.
The sentence in the exclusion criteria has been modified to consider this interesting comment.
Please see p7: “subjects who are not ready to perform the self-rehabilitation program”
[Roche N, Zory R, Sauthier A, Bonnyaud C, Pradon D, Bensmail D. Effect of rehabilitation and botulinum toxin injection on gait in chronic stroke patients: a randomized controlled study. J Rehabil Med. 2015 Jan;47(1):31-7.]

5. why stretching when there is no evidence for it?

Several consensus recommend practice stretching in context of spasticity to optimize effects of botulinum toxin injections [Wissel 2009, The Royal College of Physicians, British Society of Rehabilitation Medicine 2009]. Wissel et al (2009) published indeed an European consensus on the use of botulinum toxin type A in adult spasticity and propose stretching to increase efficacity of botulinum toxin although the modalities remain to be clarified. The Royal College of Physicians, British Society of Rehabilitation Medicine recommend, in his guideline, programme of stretching and physical therapy intervention to maintain muscle and soft tissue length across joints, facilitate care giving and facilitate active control of any residual movements. Patient’ education on stretching regimes is also recommended [Royal College of Physicians, British Society of Rehabilitation Medicine 2009]. Also, many authors recommend stretching following botulinum toxin injection [Rodriquez 2000, Carda 2011, Giovannelli 2007, Santamato 2015, Deltombe 2017]. The elements considered in favor of muscle lengthening are a motor neuron excitability reduction, increase botulinum toxin absorption,

maintain or increase soft-tissue extensibility, pain reduction and functional improvement [Bovend'Eerdt 2008, Santamato 2015].

The question of the reviewer is legitimate in view of certain publications. For example, Carda et al (2011) showed that stretching after botulinum toxin for spastic equinus foot has significant effects on spasticity assessment but not maintained at 3 months while these effects were maintained with taping and casting. The authors suggested that poorer result of stretching is explained by its shorter duration in comparison with the prolonged stretching of the muscle allowed by casting. One may wonder if 30 minutes' stretching twice a day for a week are enough to induce long-term improvements. Mills et al (2016) suggested indeed, in their review, that stretching appears less effective than casting or taping but affirm that no study assessed stretching as the sole adjunct therapy and state that the lack of superiority does not mean inefficiency. These authors recently proposed also that "As stretching is a minimally invasive and low resource intervention that is commonly prescribed, it merits further research as an adjunct therapy" following botulinum toxin injections. There is indeed a "need for taping to be checked and rearranged daily by a trained therapist and the cast also needs to be changed twice per week and takes around 30 minutes to apply, which may not be feasible in many clinical settings." Santamato et al (2015) agree with these arguments.

Another study assessed patients with spastic paraplegia who received botulinum toxin injections in triceps surae followed by daily stretching exercises during 18 weeks. Authors proposed that beneficial effects on gait velocity maintained until 18 weeks, although effects of botulinum toxin have commonly stopped, may be due to the stretching [de Niet 2015].

Finally, in their review, Bovend'Eerdt et al (2008) highlight that it is difficult to explore the effects of stretching in spasticity because of heterogeneity of the studies concerning methodology, population, intervention and outcome measures. They concluded that there is some positive evidence supporting the positive effects of a stretching session but it remains unclear how long these effects abide and their

long-term consequences.

Regarding our study, there is a set of arguments to propose stretching exercises to patients with spasticity following their botulinum toxin injections, to match current international recommendations although the level of evidence appears not obvious.

To complete the article, justifications have been added.

Please see p8:" For patients in the SR group, the program will be based on the three dimensions of rehabilitation described above: stretching, strengthening and task-oriented exercises, which correspond to current recommendations [58], [59]."

[Bovend'Eerdt TJ, Newman M, Barker K, Dawes H, Minelli C, Wade DT. The effects of stretching in spasticity: a systematic review. Arch Phys Med Rehabil. 2008 Jul;89(7):1395-406.]

[Carda S, Invernizzi M, Baricich A, Cisari C. Casting, taping or stretching after botulinum toxin type A for spastic equinus foot: a single-blind randomized trial on adult stroke patients. Clin Rehabil. 2011 Dec;25(12):1119-27.]
[Deltombe T, Wautier D, De Cloedt P, Fostier M, Gustin T. Assessment and treatment of spastic equinovarus foot after stroke: Guidance from the Mont-Godinne interdisciplinary group. J Rehabil Med. 2017 Jun 28;49(6):461-468.]
[de Niet M, de Bot ST, van de Warrenburg BP, Weerdesteyn V, Geurts AC. Functional effects of botulinum toxin type-A treatment and subsequent stretching of spastic calf muscles: a study in patients with hereditary spastic paraplegia. J Rehabil Med. 2015 Feb;47(2):147-53.]
[Giovannelli M, Borriello G, Castri P, Prosperini L, Pozzilli C. Early physiotherapy after injection of botulinum toxin increases the beneficial effects on spasticity in patients with multiple sclerosis. Clin Rehabil. 2007 Apr;21(4):331-7.]
[Mills PB, Finlayson H, Sudol M, O'Connor R. Systematic review of adjunct therapies to improve outcomes following botulinum toxin injection for treatment of limb spasticity. Clin Rehabil. 2016 Jun;30(6):537-48.]
[Rodriquez AA, McGinn M and Chappell R. Botulinum toxin injection of spastic finger flexors in hemiplegic patients. Am J Phys Med Rehabil 2000; 79: 44–7.]
[Royal College of Physicians, British Society of Rehabilitation Medicine, Chartered Society of Physiotherapy, Association of Chartered Physiotherapists Interested in Neurology. Spasticity in adults: management using botulinum toxin. National guidelines. 2009]
[Santamato A, Micello MF, Panza F, Fortunato F, Picelli A, Smania N, Logroscino G, Fiore P, Ranieri M. Adhesive taping vs. daily manual muscle stretching and splinting after botulinum toxin type A injection for wrist and fingers spastic overactivity in stroke patients: a randomized controlled trial. Clin Rehabil. 2015 Jan;29(1):50-8.]
[Wissel J, Ward AB, Erztgaard P, Bensmail D, Hecht MJ, Lejeune TM, et al. European consensus table on the use of botulinum toxin type A in adult spasticity. J Rehabil Med 2009; 41: 13–25]

6. please rewrite the methods in line with the CONSORT statement and use their flow chart
The methods has been rewritten in line with the CONSORT statement as suggested
The flow chart of CONSORT has been used
Please see p7-16

7. use a different term than thymic state - this is not used in regular English. I think you mean mood.
Terms “thymic state” have been replaced by “mood” as suggest the reviewer

8. Missingness is not a word. I think you mean missing data.
“Missingness” have been replaced by “missing data”
Please see p15

9. I think you need to be careful about interpreting the evidence of a beneficial effect of adjuvant therapies to BTI - it is more that BTI itself has limited evidence.

The discussion has been rewritten and tempered to take into consideration this comment. Please see p15: “To potentiate the effects of BTI and reduce consequences of hypertonia following stroke (spasticity, spastic dystonia, spastic co-contraction), rehabilitation in adjunction appears interesting since BTI alone seem to have limited functional positive effects on functions of patients with stroke. […]If our hypothesis of an effectiveness of self-rehabilitation to optimize the effects of BTI is validated, it would be an approach to recommend with little additional cost to the already limited health-system budget.”

10. which international trial register will this be lodged with?
Trial registration number: 02944929. ClinicalTrials.gov: NCT02944929
This information is available at the end of the abstract and had been added after the discussion of the manuscript.

VERSION 2 – REVIEW

REVIEWER	Giovanni Abbruzzese DINOGMI University of Genoa (Italy)
REVIEW RETURNED	11-Feb-2018

GENERAL COMMENTS	The Authors have clearly and satisfactorily addressed the points raised in reviewing the first submission. I do not have further comments or criticisms.

REVIEWER	Susan Hillier University of South Australia, Australia
REVIEW RETURNED	18-Mar-2018

GENERAL COMMENTS	The title needs to reflect that this is a protocol. The addition of 30min of self-rehabilitation cannot be considered "intensive". The language throughout needs extensive editing. Some terms are offensive for example "spastic patients". All participants will continue to receive usual care rehabilitation. This will likely cause less of a difference in effect as many will seek increased rehab to support their BTI spontaneously. A CONSORT compliance needs to to provided. You cannot statistically analyse qualitative data - it is narrative based. There are too many references >15 years old.This is a fast moving area and this is not appropriate. The GAS is not an appropriate primary outcome. It could be in any domain and is difficult to administer in some clients.

VERSION 2 – AUTHOR RESPONSE

Reviewer(s)' Comments to Author:

Reviewer: 1
Reviewer Name: Giovanni Abbruzzese
Institution and Country: DINOGMI, University of Genoa (Italy)
Please state any competing interests or state 'None declared': None

Please leave your comments for the authors below
The Authors have clearly and satisfactorily addressed the points raised in reviewing the first submission. I do not have further comments or criticisms.

Reviewer: 2
Reviewer Name: Susan Hillier
Institution and Country: University of South Australia, Australia
Please state any competing interests or state 'None declared': None declared

Please leave your comments for the authors below

The title needs to reflect that this is a protocol.
The title has been changed to reflect the protocol.
Please see p1: "Effects of a 6 months self-rehabilitation program in addition to botulinum toxin injections and conventional physiotherapy on limitations of patients with spastic hemiparesis following stroke. Adju-Tox : protocol for a multicentre, randomised controlled, investigator blinded study."

The addition of 30min of self-rehabilitation cannot be considered "intensive".
What we considered as intensity means not only the duration of rehabilitation per day but also a rehabilitation 7 days out of 7 for 6 months without interruption. This appears more intensive than the 1.7 sessions of 20-30minutes of physiotherapy per week, conventionally followed by chronic patients with stroke living at home. Similarly, Sun et al (2010) proposed an intensive specific rehabilitation for 2 hours/day but only 3 days/week for 3 months, which could correspond to what is proposed in our study.
We propose, in the present study, to increase the intensity with 30minutes of rehabilitation focusing on specific goals in addition to the standard rehabilitation and daily activities of patients. The specificity of these 30 minutes of self-rehabilitation is that exercises are especially chosen to meet the goal jointly determined by the patient and the doctor to optimize the effects of toxin injections, which contrast with less intensive and not specific rehabilitation.

To take in consideration the comment of the reviewer, the term "intensive rehabilitation" has been deleted when needed and sentences have been modified.
Please see p5: "A self-rehabilitation program appears a relevant approach to increase the intensity of the oriented needed rehabilitation and further improve recovery of these patients."
Please see p6:" To increase the intensity of the oriented rehabilitation following BTI would be indeed relevant."
Please see p6:" Results of these pilot studies with restricted sample suggest effectiveness of adding sessions of specific exercises following BTI in patients with stroke, which corresponds to the conclusions of two recent reviews [55], [56].
Please see p6:" All previous results leads us to the hypothesis that the addition of a specific 30 minutes self-rehabilitation program to repeated BTI and usual physiotherapy should increase…."
Please see p15:" Results of these pilot studies suggest effectiveness of adding specific and more intensive therapy following BTI in patients with stroke."

[Sun SF, Hsu CW, Sun HP, Hwang CW, Yang CL, Wang JL. Combined botulinum toxin type A with modified constraint-induced movement therapy for chronic stroke patients with upper extremity spasticity: a randomized controlled study. Neurorehabil Neural Repair. 2010 Jan;24(1):34-41. doi: 10.1177/1545968309341060.]

The language throughout needs extensive editing. Some terms are offensive for example "spastic patients".
We thank the reviewer; we did not think these terms were offensive.
Terms have been deleted and sentences have been corrected.

Please see the Abstract: “Home-based self-rehabilitation programs combined with botulinum toxin injections (BTI) appear to be a relevant approach to increase the recommended intensive rehabilitation of patients with spasticity following a stroke.”
“The aim of this study is to assess the effects of a 6-months self-rehabilitation program in adjunction to BTI, in comparison with BTI alone, to reduce limitations of patients with spasticity following a stroke.”
Please see p6:” The aim of this study is to assess the effects of a 6-months self-rehabilitation program in adjunction to BTI, in comparison with BTI alone, to reduce limitations of patients with spasticity having a stroke.”

All participants will continue to receive usual care rehabilitation. This will likely cause less of a difference in effect as many will seek increased rehab to support their BTI spontaneously.
Most of chronic patients with stroke living at home usually continue to receive rehabilitation sessions and continue to practice functional activities to maintain their capacities. Patients who will be included in this study regularly benefit of botulinum toxin injections to reduce their spasticity and awkward consequences. These patients continue their rehabilitation sessions in parallel with their injections. It would not be ethical to tell patients to stop their usual rehabilitation for the 6 months of this study. Moreover, we stipulate to patients that they should not inform their city physiotherapist of their inclusion in the protocol (and thus not say their primary goal aimed with injected muscles and specific exercises related for patients in self-rehab group). Physiotherapy should be continued as previously. The only one modification in the patients follow up is the complete assessment before and after BTI and the self-rehabilitation for patients of this group. For patients who will not respect this guideline or patients who would like to support their BTI spontaneously, we can hypothesize that this potential effect would be the same in both groups.
To take in consideration the comment of the reviewer, a sentence was added in the method section.
Please see p8: “All patients will be able to continue their usual physiotherapy. However we stipulate to the patients not to inform their physiotherapist of their participation to the study not to change their usual care.”

A CONSORT compliance needs to to provided.
We provided the Consort Compliance

You cannot statistically analyse qualitative data - it is narrative based.
We have reworded the sentence and clarified that these statistical analyses refer to "categorial" data instead of "qualitative" data, as "qualitative" may indeed be misunderstood as related to textual data from interview transcriptions, which is not the case in our study.
Please see p14: “Categorial data will be compared by means of Chi-square tests or Fisher exact tests.”

There are too many references >15 years old. This is a fast moving area and this is not appropriate.
Some of the older references have been deleted whether they justified text in addition to another more recent reference. Some older references have been replaced by more recent.
Please see References p16.
Some old references which appear as main, unavoidable bibliographic sources need to be conserved such as:
- World Health Organization in *Stroke 1989* for the definition of stroke
- Twitchell *in Brain in 1951* for “The restoration of motor function following hemiplegia in man published”
- Perry *in Stroke in 1995,* for “Classification of walking handicap in the stroke population”.
Also, gait characteristics of patients with stroke are studied for many years and have not changed since, which explain some old unavoidable references at the beginning of the introduction.
The comment of the reviewer has been taken into consideration and all references have been checked.

The GAS is not an appropriate primary outcome. It could be in any domain and is difficult to administer in some clients.
Most of studies assessing the effects of botulinum toxin injections in patients with stroke demonstrated their benefits at the level of impairment and gait kinematics but the evidence for functional benefit is less clear [Simpson 2000, Smith 2000, Wissel 2000, Robertson 2009]. The use of standardized outcomes with inadequate sensitivity for assessing changes in functional disability is the

argument put forward to explain this [Richardson 2000]. Also, there is often a discrepancy between significant improvement in patient's global assessment (subjective rating of problem severity) and scores on standardized measures [Smith 2000, Richardson 2000]. Similarly Lagalla et al (2000) found no change for disabilities but achievement of the goal of self-care for patients following repeated botulinum toxin injections in upper limb.
It could be argued that conventional functional scales are not representative of needs, are not sensitive enough and/or do not correspond to the patients' expectations, especially for upper limb. Brashear et al (2000) published in The New England Journal of Medicine a study on the effects of BTI in 126 subjects with stroke in a randomized, double-blind, placebo-controlled, multicenter trial. They proposed as primary outcome measure a self-reported disability scale considering 4 areas (dressing, hygiene, limb position and pain). Patients had to report their disabilities in the principal target of treatment. Significant improvements in selected area of functioning, corresponding to patients 'goal, were found for patients treated with BTI. Similarly Wissel et al (2000) used a Rating of Response to botulinum toxin consisted of patients' self-assessment of pain and function. They highlighted its relevance in measurement of botulinum toxin effects.
In the same line, Ashford and Turner-Stokes proposed the Goal Attainment Scaling for spasticity management using botulinum toxin and found that GAS provides a useful measure of functional gains in response to treatment with botulinum toxin [Ashford 2006].
In accordance with all these previous publications, we have chosen the GAS to assess the effects of botulinum toxin injections (and self-rehabilitation) on functional limitations. We agree with the reviewer that original GAS could consider any domain and could appear too broad. To limit this heterogeneity in goals, we defined areas and goals of GAS among which therapists and patients must choose and establish scores according to the needs of the patient. These restricted domains are presented in Appendix of the article. Our choice of outcome and domains of goals are in accordance with areas of disabilities studied by Brashear et al for which they obtained positive results.
Other standardized conventional outcomes such as 10meters walking test, Timed Up and go, Action Research Arm test are also used in our study. Results of this study would be discussed in regard to the primary outcome GAS and conventional functional tests.
The French community of physical medicine and rehabilitation (17 centers involved in this study) approved the choice of the GAS to evaluate the personalized goals which represent routine practice with patients followed in medical consultation to reduce their spasticity and consequences.
Concerning the comment of the reviewer about the difficulty to administer the GAS in some clients, we exclude patients with cognitive deficits who do not understand the instructions, anosognosic patients.
The present study was built with GAS as the primary outcome, with the calculation of the corresponding sample size.
To consider the comment of the reviewer, the text has been modified in the method section.
Please see p 9: "According to previous studies, standardized outcomes appear to have an inadequate sensitivity and to be not representative of patients' needs for assessing changes in functional disability following botulinum toxin injections [34], [47], [48]. In contrast GAS appears more sensitive, provides an accurate indication of success in relation to the intended goals of upper and lower limbs spasticity treatment and, strongly correlated with its reduction (evaluated with the modified Ashworth scale, most widely used scale) [34], [35].

[Ashford S, Turner-Stokes L. Goal attainment for spasticity management using botulinum toxin. Physiother Res Int 2006;11:24–34.]
[Brashear A, Gordon MF, Elovic E, Kassicieh VD, Marciniak C, Do, M, Lee C et al. Intramuscular injection of botulinum toxin for the treatment of wrist and finger spasticity after a stroke. New England Journal of Medicine 2000; 347: 395–400]
[Robertson JV, Pradon D, Bensmail D, Fermanian C, Bussel B, Roche N. Relevance of botulinum toxin injection and nerve block of rectus femoris to kinematic and functional parameters of stiff knee gait in hemiplegic adults. Gait Posture. 2009 Jan;29(1):108-12.]

[Lagalla G, Danni M, Reiter F, Ceravolo MG, Provinciali L. Post-stroke spasticity management with repeated botulinum toxin injections in the upper limb. Am J Phys Med Rehabil 2000;79:377-84.]
[Richardson D, Sheean G, Werring D, et al. Evaluating the role of botulinum toxin in the management of focal hypertonia in adults. J Neurol Neurosurg Psychiatry 2000;69:499-506.]
[Simpson DM, Alexander DN, O'Brien CF, et al. Botulinum toxin type A in the treatment of upper extremity spasticity: a randomized, doubleblind, placebo-controlled trial. Neurology 1996;46:1306-10]
[Smith SJ, Ellis E, White S, Moore AP. A double-blind placebo-controlled study of botulinum toxin in upper limb spasticity after stroke or head injury. Clin Rehabil 2000;14:5-13.]
[Wissel J, Muller J, Dressnandt J, et al. Management of spasticity associated pain with botulinum toxin A. J Pain Symptom Manage 2000;20:44-9.]